

REMARKS

I. Disposition of claims

Claims 1-10, 12-18 and 21 are pending. Claim 11 has been canceled and new claim 21 has been added. The election of species requirement of record has been made final. Claim 6, 7 and 14 are withdrawn from consideration. Claims 1-5, 8-10, 12, 13, 15-18 and 21 are under examination.

II. Claim amendments

Applicants submitted a response on 10 July 2009 to the final Office Action mailed 5 June 2009. In that response, Applicants amended independent claims 1 and 5 to clarify that the claimed invention is directed to the administration of an aqueous suspension *via a gastric tube* to a pediatric patient. As such, administration of the aqueous suspension by “syringe” was deleted from claims 1 and 5.

In the Advisory Action mailed 15 July 2009, the Examiner stated that the response will not be entered because the claim amendment raises new issues that would require further consideration and/or search. Specifically, on page 2 of the Advisory Action, the Examiner stated that the claim amendment “alters the scope of the claims by requiring oral administration of the aqueous suspension via gastric tube as opposed to by gastric tube or syringe”.

Applicants do not wish to have the unentered response, filed 10 July 2009, entered.

In this Amendment, the expression “or syringe” has again been deleted from independent claims 1 and 5. This time, however, the word “oral” has been deleted from independent claims 1, 5 and 16 to clarify that the invention, as defined by the amended claims, excludes oral administration.

As provided by the specification at page 4, lines 15-17, an object of the invention is to provide an improved and robust method for administering a composition comprising enteric coating layered pellets of a proton pump inhibitor *via a gastric tube*. By definition, gastric tube feeding is a type of enteral feeding:

Enteral

- by mouth (orally), many drugs as tablets, capsules, or drops;
- by gastric feeding tube, duodenal feeding tube, or gastrostomy, many drugs and enteral nutrition; and
- rectally, various drugs in suppository or enema form.

(See Route of administration – Definition:

http://www.wordiq.com/definition/Route_of_administration)

Examples of feeding tubes include naso-gastric tubes and gastric feeding tubes. A nasogastric feeding tube, or "NG-tube", is passed through the nares, down the esophagus and into the stomach. A gastric feeding tube (or "G-tube," or "button") is a tube inserted through a small incision in the abdomen into the stomach. Feeding tube – from Wikipedia http://en.wikipedia.org/wiki/Gastric_feeding_tube. The purpose and function of enteral feeding by gastric feeding tube is to by-pass the oral cavity and thereby avoid chewing and swallowing to obtain nutrition and hydration.

Applicants submit that the claim amendments are (a) of a clarifying nature, (b) fully supported by the specification as originally filed (p. 16, lines 19-28) and (c) consistent with accepted definitions in the pharmaceutical industry. Specifically, gastric tube feeding, e.g., by a NG-tube or G-tube, is a type of enteral feeding which is distinguishable from administration by mouth (orally) of tablets, capsules, drops, etc.

Upon request from the Examiner, Applicants will similarly amend the specification by deleting instances of the word "oral", where appropriate, so that the written description is commensurate with the amended claims.

For the sake of consistency, claim 11 has been deleted because that claim recites a gastric tube size from CH 10 to CH 20 which is suitable for an adult population (See p. 16, lines 24-25) whereas the claimed method is directed to the treatment of a pediatric population. Claim 12 recites a gastric tube size from CH 5 to CH 10 which is consistent with the treatment of a pediatric population (See p. 16, lines 27-28). Similarly, claim 13 has been amended to recite a dose of the active substance that is suitable for a pediatric population and new claim 21 has been added to recite a preferred dose for pediatric use (See p. 17, lines 6-8).

The claim amendments clarify that the claimed invention is directed to a nonoral route of administration to a pediatric population. No new matter has been introduced by the claim amendments.

III. Claim rejections – 35 U.S.C. §103

a. Olovson + Bergstrand

Claims 1-5, 8, 9, 12, 13 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/25070 (hereinafter “Olovson”) in combination with US 5,753,265 to Bergstrand et al. (“Bergstrand”).

All claims under examination are expressly characterized by the administration of an aqueous suspension comprising a multiple of enteric coating layered pellets *via a gastric tube* to a pediatric population. In accordance with claims 1 and 16, the aqueous suspension is comprised of a solid composition dispersed in an aqueous carrier, wherein the solid composition comprises a therapeutically effective amount of an acid labile proton pump inhibitor (“PPI”) in the form of a multiple of enteric coating layered pellets in admixture with at least one pharmaceutically acceptable thickener. Alternatively, in accordance with claim 5, the enteric coating layered pellets are dispersed in a viscous aqueous medium.

Surprisingly, Applicants have found that the higher the viscosity of the aqueous suspension of the claimed invention the thinner the gastric tubes can be used within certain limits (p. 5, lines 8-12). Therefore, pursuant to the claimed invention, the viscous dispersing medium enables the enteric coated pellets to float within the medium (p. 5, lines 15-16). Advantageously, this so-called “floating” property facilitates and improves the administration to young children by permitting thinner tubes to be used without clogging of the enteric coated pellets in the tubes (p. 5, lines 17-21).

At page 4 of the Office Action, the Examiner acknowledges that Olovson does not disclose a PPI dosage of 1-100 mg or the administration of an aqueous suspension of enteric coated PPI pellets to a pediatric population. For this purpose, the Examiner relies on Bergstrand and alleges that Bergstrand discloses an aqueous dispersion of enteric coated layered units which is suitable for administration through a naso-gastric tube to a pediatric population and/or to

patients with swallowing disorders. The Examiner concludes that it would have been obvious, at the time the claimed invention was made, to administer the composition taught by Olovson with a thickener to a pediatric population.

The Examiner's reliance on Bergstrand assumes that the primary reference to Olovson discloses the administration of a composition comprising a thickener and a PPI in the form of enteric coating layered pellets *via a gastric tube*. This assumption is incorrect and, therefore, there is no motivation to combine Olovson with Bergstrand, since Olovson in fact teaches against the use of naso-gastric tubes. For the following reasons, Applicants respectfully disagree with the Examiner and submit that neither Olovson nor Bergstrand discloses or suggests the administration of a composition comprising a thickener and a PPI in the form of enteric coating layered pellets via a gastric tube to a pediatric population as claimed.

Specifically, as background to Olovson, it is disclosed that anti-ulcer compounds such as histamine-2-receptor antagonists were administered to horses by naso-gastric tubes (p. 1, lines 28-31). However, at the time the invention claimed by Olovson was made, it was known that the use of naso-gastric tubes was traumatic to the animal and required sedation and trained personnel to assist in the administration. To avoid these known disadvantages, Olovson provides a paste-like gel having a sufficiently thick consistency permitting oral administration of a dose, e.g., by a syringe, onto the dorsal end of the animal's tongue for swallowing, thereby avoiding the use of gastric tubes (p. 8, lines 8-9). Applicants submit, therefore, that Olovson actually teaches against the use of gastric tubes in favor of direct oral administration of the paste-like gel to eliminate trauma to the animal and avoid the need for sedation and trained personnel.

Moreover, the secondary reference to Bergstrand represents the known disadvantages of the prior art at the time the claimed invention was made. As noted by the Examiner, Bergstrand discloses an aqueous dispersion of enteric coated layered units which is suitable for administration through a naso-gastric tube. Although having advantages, administration of enteric coated pellets through a gastric tube as disclosed by Bergstrand - *without a thickener* - has its own disadvantages as disclosed in the specification at page 3, lines 18-25:

- Problems that might arise with administration of enteric coated pellets through gastric tube are for instance caused by the size of the enteric coating layered pellets and the inner

diameter the tube or the outlet of the syringe, which might cause clogging in the syringe or tube. This is especially critical for pediatric patients where thin tubes are often required.

- There is also a risk of reduced patient compliance and non-complete dose delivery because of pellets sediment in the glass and/or clogging the syringe used when preparing the suspension. This is especially critical in pediatric use when working with small volumes and doses.

In summary, Applicants submit that the intended purpose and function of the primary reference to Olovson is to provide a solution to the disadvantages associated with the administration of anti-ulcer compounds to horses by naso-gastric tubes. That solution is the oral administration of a paste-like gel comprising a PPI in the form of beads via a syringe (See claim 17). As such, Olovson clearly teaches against the use of gastric tubes and, therefore, there is no motivation to combine Olovson with Bergstrand. Furthermore, Bergstrand represents the disadvantages associated with prior art methods for administering enteric coated pellets through a gastric tube. Bergstrand offers no hint that a thickener or viscous medium would permit the use of narrower gastric tubes which is particularly advantageous with a pediatric population. In any event, neither Olovson nor Bergstrand discloses or suggests the administration of a composition comprising a thickener and a PPI in the form of enteric coating layered pellets via a gastric tube to a pediatric population as claimed.

For all of the forgoing reasons, a *prima facie* case of obviousness has not been established. Withdrawal of the §103 rejection is requested.

b. Olovson + Bergstrand + Calanchi

Claims 1-5, 8, 9, 12, 13 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olovson and Bergstrand further in view of US 6,261,602 to Calanchi et al. (“Calanchi”).

Calanchi discloses a sachet dosage form prepared from a base granular product made by subjecting one or more thickening agents and one or more disintegrating agents to wet or dry granulation (See claim 1). The granular product is used as a pharmaceutical carrier of

pharmaceutical compositions that are capable of rapid suspension in water or aqueous media including saliva. The compositions may be used by addition to a glass of water with stirring or taken directly in the mouth (See Abstract; col. 6, lines 1-8).

For the reasons of record, Applicants maintain that Calanchi teaches away from the claimed invention. The express purpose of the claimed invention is to provide a solution to the clinical problems associated with the oral administration of enteric coated pellets of a PPI to pediatric patients who are suffering from a gastrointestinal disorder and who may also have difficulties swallowing. For this pediatric population, administration of tablets, capsules or pellets mixed with soft foods or juices is not an option (See p. 2, line 26 to p. 3, line 16).

Applicants strongly disagree with the Examiner's statement on page 7 of the Office Action that there is a "small difference" between oral administration, e.g., drinking as disclosed by Calanchi, and administration by a gastric tube as claimed. As discussed in Section II, above, oral administration and gastric tube feeding are classified as distinguishable types of enteral feeding:

Enteral

- by mouth (orally), many drugs as tablets, capsules, or drops, and
- by gastric feeding tube, duodenal feeding tube, or gastrostomy, many drugs and enteral nutrition.

(See Route of administration – Definition:

http://www.wordiq.com/definition/Route_of_administration)

It is evident that the purpose and function of enteral feeding by gastric feeding tube, e.g., NG-tube, G-tube, etc., is to by-pass the oral cavity and thereby avoid chewing and swallowing to obtain nutrition and hydration.

Therefore, it is clinically erroneous to include gastric tube feeding with oral administration, e.g., from a glass, poured in directly into the mouth or introduced into the mouth via syringe, as the Examiner has done on page 7 of the Office Action. Similarly, in view of the complex differences between normal swallowing physiology and swallowing disorders indicating administration of enteral nutrition by a feeding tube, it is also clinically erroneous to say that there is a "small difference" between oral administration and administration by a feeding

tube as the Examiner has done on page 7 of the Office Action. Since it is clinically incorrect to equate oral administration with enteral feeding by gastric tube, then it is also incorrect from an obviousness and patentability standard.

Thus, the administration routes disclosed by Calanchi - the pharmaceutical composition is poured directly into a glass of water for drinking or poured directly in the mouth for swallowing - are inapposite to the administration route of the claimed invention through a gastric tube. As such, there would have been no motivation at the time the claimed invention was made to consider Calanchi in the development of a method for administering a composition comprising a thickener and a PPI in the form of enteric coating layered pellets via a gastric tube to a pediatric population who may have difficulties swallowing.

Moreover, Calanchi does not overcome the fundamental failure of the combination of Olovson and Bergstrand to establish a *prima facie* case of obviousness for the reasons given in Section III(a), above. Olovson clearly teaches against the use of naso-gastric tubes. Bergstrand represents the disadvantages associated with prior art methods for administering enteric coated pellets through a gastric tube. Bergstrand offers no hint that a thickener or viscous medium would permit the use of narrower gastric tubes which is particularly advantageous with a pediatric population. Therefore, whether taken alone or in combination, none of Olovson, Bergstrand or Calanchi discloses or suggests the administration of a composition comprising a thickener and a PPI in the form of enteric coating layered pellets via a gastric tube to a pediatric population as claimed.

Withdrawal of the § 103 rejection based on the combination of Olovson, Bergstrand and Calanchi is requested.

c. Olovson + Bergstrand + Mulchandani

Claims 1-5, 8-13 and 15-18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Olovson and Bergstrand and further in view of US 5,108,767 to Mulchandani et al. ("Mulchandani").

For the reasons given in Section III(a), above, Olovson does not teach or suggest the use of a gastric tube for application of the composition disclosed by Olovson onto the dorsal end of

an animal's tongue. At the time the invention claimed by Olovson was made, it was known that naso-gastric tubes were disadvantageous in the delivery of pharmaceutical compositions to a horse. To avoid the use of gastric tubes, Olovson developed a paste like gel that could be orally delivered by syringe onto the dorsal end of the horse's tongue. And it is irrelevant that Bergstrand discloses the use of naso-gastric tubes with a pediatric population and/or patients with swallowing disorders. There is no motivation to combine Bergstrand with Olovson in view of the intended purpose and function of Olovson to provide an oral administration regimen replacing the use of gastric tubes and thereby eliminating trauma to the animal and avoiding the need for sedation and trained personnel.

It is no surprise, therefore, that Olovson - as correctly noted by the Examiner on page 7 of the Office Action - does not disclose a diameter of any feeding tube. The Examiner's reliance on Mulchandani and the disclosure of feeding tubes size 8 French or larger is misplaced. As previously stated, Olovson provides a paste-like gel having a sufficiently thick consistency permitting oral administration of a dose onto the dorsal end of the animal's tongue for swallowing thereby avoiding the use of gastric tubes. Accordingly, there is no motivation to modify Olovson by combining that reference with Bergstrand and/or Mulchandani.

Therefore, Mulchandani does not overcome the fundamental failure of the combination of Olovson and Bergstrand to establish a *prima facie* case of obviousness for the reasons given in Section III(a), above. For all of the foregoing reasons, the §103 rejection based on the combination of Olovson, Bergstrand and Mulchandani is improper and withdrawal thereof is requested.

CONCLUSION

Applicants have made a good faith attempt to respond to the Office Action. For all of the foregoing reasons, claims 1-5, 8-10, 12, 13, 15-18 and 21 are in condition for allowance, which action is earnestly solicited. In view of the allowability of the elected claims, withdrawal of the election of species requirement as to claims 6, 7 and 14 is also requested.

Any fees due in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: 21 August 2009

Respectfully submitted,
/John M. Genova/
John M. Genova
Reg. No. 32,224

Customer No. 007470
Direct Dial: (212) 819-8832